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FROM PITT-ROGERS-DANKS SYNDROME TO WOLF-HIRSCHHORN SYNDROME. AND BACK?

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Apparently normal chromosomes without a molecular 4p16.3 deletion were found in a patient with a Wolf-Hirschhorn syndrome (WHS) phenotype. During a 10-year-period of observation he consistently presented with typical facial appearance, moderate to severe mental retardation, normal physical development with normal head circumference.
Genetic results and the relatively mild clinical manifestations suggest that a diagnosis of Pitt-Rogers-Danks syndrome (PRDS) may be more likely in this patient. If WHS and PRDS will ultimately prove to be caused by haploinsufficiency of the same gene in 4p16, non-deleted patients such as the present one will be good candidates for the search of point mutations in such putative gene.

KEY WORDS: aneuploidy syndrome, fluorescent *in situ* hybridization, Wolf-Hirschhorn syndrome, Pitt-Rogers-Danks syndrome.

INTRODUCTION

Pitt-Rogers-Danks (PRDS) and Wolf-Hirschhorn (WHS) syndromes are recognizable clinical entities comprising mental retardation, pre- and post-natal growth retardation, microcephaly, seizures and characteristic facial appearance with maxillary hypoplasia, proptosis, hypertelorism, short and flat philtrum and peculiar nose. In addition to the shared clinical manifestations, a beaked nose with large nasal bridge and a wide mouth with poorly defined upper lip are more consistent with a PRDS diagnosis, while a "Greek helmet" midfacial appearance is considered typical of WHS.

A 4p16.3 deletion is detectable in WHS at a cytogenetic or molecular level, while all the patients originally described as PRDS have had apparently normal chromosomes.

Based on these considerations, PRDS and WHS were thought to be distinct genetic entities. However, this clinical distinction is questioned by the report of Clemens et al. [1996], who note in a patient a changing phenotype from one typical of PRDS to the "Greek helmet" facial appearance, suggestive of WHS. More importantly, a 4p16.3 deletion has now been detected at a molecular level in 6 of 7 patients previously diagnosed as PRDS [Clemens et al., 1996; Lindeman-Kusse et al., 1996].

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These data raise the question whether PRDS and WHS should still be considered different conditions.

In this issue of the journal, Donnai suggests that all PRDS patients with 4p deletion should be considered as having WHS, whereas at the moment the clinico-molecular correlation for the nondeleted *PRDS/WHS* cases remains doubtful.

We report on a PRDS/WHS patient without a detectable 4p16.3 deletion and discuss the relevant nosological issues.

CLINICAL REPORT

S.R., a male born in 1984, is the third child of nonconsanguineous parents. One brother died *in utero* of asphyxia. The patient was born at 38 weeks of gestation by normal delivery. Birthweight was 3300 g.

Reportedly, congenital hypotonia was present.

We first saw the patient at 12 months, and repeatedly until age 10 years. He walked unsupported at 24 months, and spoke single words at about 16 months. Bilateral cryptorchidism was corrected surgically at 3 years.

In the first 6 years, his height was between the 25th and the 50th centile, weight between the 3rd and the 25th centile and head circumference (OFC) at the 10th centile. At 10 years, his height was 140 cm (50th-75th centile) weight 35 kg (75th centile), and OFC 52.5 cm (25th-50th centile). Clinical manifestations included mental retardation of moderate to severe degree, peculiar face with high forehead, prominence of the metopic suture and of the glabella, proptosis with apparent hypertelorism, downslanting palpebral fissures, epicanthic folds, "Greek helmet" appearance of the midface, short upper lip, and micrognathia [Fig. 1]. He has a transverse palmar crease bilaterally and fingertip dermatoglyphics are A, A, Lu, W, Lu on right and Lu, A, Lu, Lu, Lu on left. Radio-ulnar synostosis was present on the right. He never had seizures. Brain CT scan and heart sounds were normal.

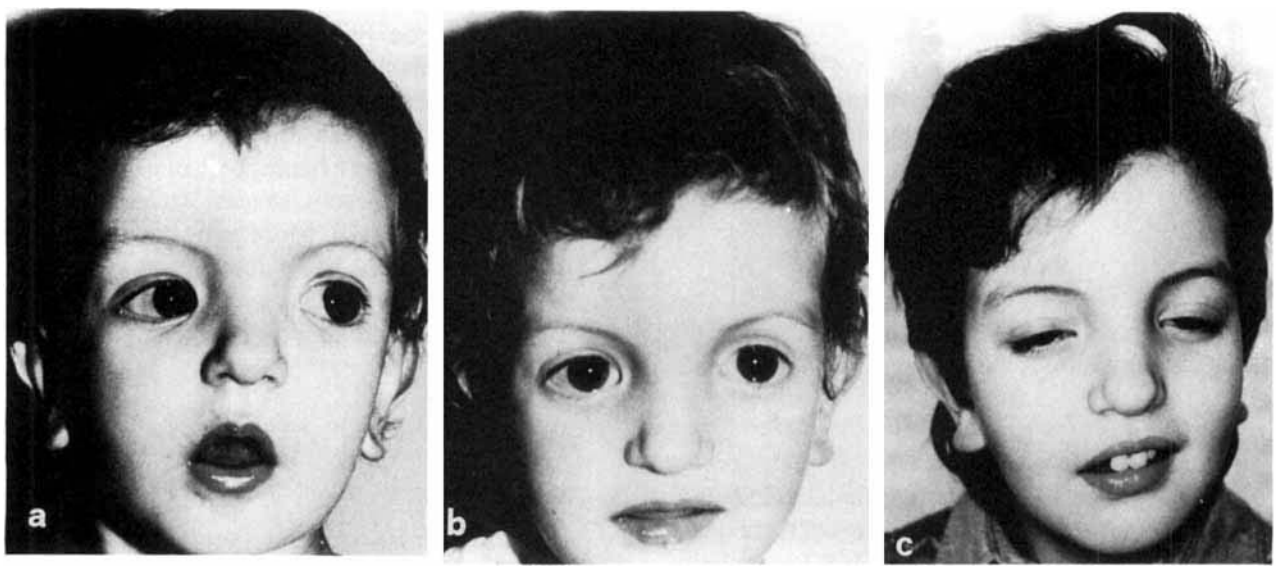

Fig. 1. a) The patient at age 12 months. Facial appearance is consistent with WHS. b) and c) The patient at 3 and 10 years, respectively. Note progressive change of facial phenotype still suggestive of WHS.

Based on these phenotypic findings, a diagnosis of WHS was considered. However, high resolution cytogenetic analysis with R(RBG) banding showed a normal male karyotype. With fluorescent *in situ* hybridization (FISH) no deletion was found using the commercially available probe D4S96 (ONCOR) corresponding to the WHS critical region [Gandelman et al., 1992].

DISCUSSION

PRDS and WHS are clinically recognizable syndromes that have been so far considered different genetic entities. Based on phenotype, a WHS diagnosis could be considered certain in our patient, at least at an early age. However, FISH analysis with a probe lying within the WHS critical region showed that he was not deleted at the 4p16.3 locus. To the best of our knowledge, only one patient is reported with typical WHS, in which a different deletion, ending about 1 Mb proximal to D4S96, was described [Wright et al.,1995]. However, any deletion outside the D4S96 locus is considered unlikely in our patient, based on the clinico-molecular correlations established by Estabrooks et al. [1995].

A 4p deletion has now been reported in 6 of 7 patients initially diagnosed as PRDS , by use of the same D4S96 probe [Clemens et al., 1996; Lindeman-Kusse et al., 1996], thus raising the question whether PRDS should be considered as a mild form of WHS. On average, patients reported as PRDS were less severely affected than WHS patients with respect to degree of mental retardation, the frequency of congenital heart defects and clefting of palate [Clemens et al, 1996].

In view of the difficulties in establishing precise clinico-molecular correlations in PRDS and WHS, even after the report of these recent findings, Donnai [1996] proposes the conservative hypothesis that all deleted PRDS patients should be considered as having WHS. Additionally, one could suggest that the nondeleted WHS patients have PRDS, with the understanding that they may turn out to have a point mutation in a putative PRDS/WHS gene.

Our patient undoubtedly presents with a very mild form of WHS. Change of facial phenotype was noted with age; he never had seizures, height, OFC and heart are normal, but psychomotor delay is moderate to severe. For these reasons, and because of the absence of a microdeletion in the WHS critical region, he is a good candidate to test for the presence of a point mutation, once the putative PRDS/WHS gene is identified.

Until then, the debate on splitting or lumping PRDS and WHS cannot be satisfactorily resolved.

REFERENCES

Clemens M, Martsolf JT, Rogers JG, Mowery-Rushton P, Surti U, McPherson E (1996):Pitt-Rogers-Danks syndrome: The result of a 4p microdeletion. Am J Med Genet, this issue.

Donnai D (1996): Editorial comment. Pitt-Rogers-Danks syndrome and Wolf-Hirschhorn syndrome. Am J Med Genet, this issue.

Estabrooks LL, Rao WR, Driscoll DA, Crandall BF, Dean CS, Ikonen E, Korg B, Aylsworth S (1995): Preliminary phenotypic map of chromosome 4p16 based on 4p deletions. Am J Med Genet 57: 581-586.

Gandelman KY, Gibson L, Meyn MS, Yang-Feng L (1992): Molecular definition of the smallest region of deletion overlap in the Wolf-Hirschhorn syndrome. Am J Med Gene 51: 571-578.

Lindeman-Kusse MC, Van Haeringen A, Hoorweg JJG, Brunner HG (1996) : Cytogenetic abnormalities in two new patients with Pitt-Rogers-Danks phenotype. Am J Med Genet, this issue.

Wright TJ, Denison K, Altherr MR (1995): Redefinition and molecular analysis of the critical region for the Wolf-Hirschhorn syndrome locus. Am J Hum Genet 57 (suppl): A233.